

IN THE CLAIMS

Claims 1 and 2 (Cancelled)

3 (Currently amended). A synthetic anti-inflammatory peptide of IL-2 and an anti-inflammatory derivative thereof or peptide derivative according to claim 1 or 2, which inhibits in vitro: (i) adhesion of activated T cells to fibronectin, laminin and/or collagen-type IV; (ii) chemotactic migration of T cells through fibronectin; and/or (iii) spontaneous or TNF- α -induced secretion of IL-8 or IL-1 β , from intestinal epithelial cells.

4 (Currently amended). A synthetic peptide according to ~~any one of claims 1 to 3~~ claim 3, selected from:

(i) peptides pep1, pep2, and pep3 of the sequences:

(pep1) Ile-Val-Leu

(pep2) Glu-Phe-Leu-Asn-Arg-Trp-Ile-Thr (SEQ ID NO:1)

(pep3) Arg-Met-Leu-Thr (SEQ ID NO:2)

(ii) peptides obtained from pep2 by deletion of one or more amino acid residues;

(iii) peptides obtained by addition to peptides (i) or (ii) of one or more natural or non-natural amino acid residues to the N-terminus and/or C-terminus;

(iv) peptides obtained by replacement of one ~~or more~~ amino acid residues residue of peptides (i) to (iii) ~~by the corresponding D-stereomer~~, by another natural amino acid residue or by a non-natural amino acid residue;

(v) peptides of (i) to (iii) which are all-L, all-D or a combination of D- and L- amino acid residues.

~~(iv)~~ (vi) chemical derivatives of the peptides (i) to ~~(iv)~~ (v);

~~(vi)~~ (vii) cyclic derivatives of peptides (i) to ~~(iv)~~ (vi);

~~(vii)~~ (viii) dual peptides consisting of two of the same or different peptides (i) to ~~(vi)~~ (vii), wherein the peptides are covalently linked to one another directly or through a spacer; and ~~(viii)~~ (ix) multimers comprising a number of the same or different peptides (i) to ~~(vi)~~ (vii).

Claim 4 (Cancelled)

5(Withdrawn as non-elected species). The synthetic peptide Ile-Val-Leu (**pep1**) and derivatives thereof according to claim 4, obtained by:

(a) elongation by up to 3-4 further amino acid residues at the N- and/or C-terminal, preferably according to the natural sequence of IL-2;

(b) substitution of the Ile residue by a natural or non-natural amino acid hydrophilic polar neutral or negatively charged, or hydrophobic non-polar neutral amino acid residue, preferably selected from Glu, Asp, Asn, Gln, Ala, Val;

(c) substitution of the Val residue by a hydrophobic, non-charged natural or non-natural amino acid residue, preferably selected from Ala, Ile, Leu, Met, Nle, Phe;

(d) substitution of the Leu residue by a hydrophobic, non-charged natural or non-natural amino acid residue, preferably selected from Ala, Ile, Met, Nle, Phe, Val;

(e) amidation of the C-terminal Leu residue,

(f) cyclization of **pep1** or of any peptide of (a) to (e); and

(g) any combination of (a) to (f).

6(Withdrawn as non-elected species). A synthetic peptide according to claim-5, selected from:

(**pep1**) Ile-Val-Leu

(**pep4**) Asn-Ile-Asn-Val-Ile-Val-Leu (SEQ ID NO:3),

(**pep5**) Ile-Val-Leu-Glu-Leu-Lys-Gly (SEQ ID NO:4),

(**pep6**) Asn-Val-Ile-Val-Leu (SEQ ID NO:5)
(**pep7**) Ala-Val-Leu
(**pep8**) Ile-Ala-Leu
(**pep9**) Ile-Val-Ala
(**pep10**) Glu-Val-Leu
(**pep11**, linear) and (**pep12**, cyclic) Cys-Ile-Val-Leu-Ala-Cys
(SEQ ID NO:6) and,
(**pep13**, linear) and (**pep14**, cyclic) Cys-Ile-Val-Leu-Ala-Ala-Cys
(SEQ ID NO:7).

7 (Currently amended). The synthetic peptide Glu-Phe-Leu-Asn-Arg-Trp-Ile-Thr (SEQ ID NO:1) (**pep2**), and derivatives thereof according to claim 4, obtained by:

(a) elongation at the C- and/or N-terminal ends by up to 4 further amino acid residues total at the C- and/or N-terminal ends, preferably according to the natural sequence of IL-2;

(b) substitution of the Glu residue by a natural or non-natural charged or polar charged amino acid residue, preferably selected from Lys, Arg, Asp, Gln, Asn;

(c) substitution of the Phe residue by a natural or non-natural hydrophobic aliphatic or aromatic amino acid residue, preferably selected from Ala, Val, Ile, Leu, Tyr, Trp, Phe, Met, Nle;

(d) substitution of the Leu residue by a natural or non-natural hydrophobic aliphatic or aromatic amino acid residue, preferably selected from Ala, Val, Ile, Leu, Tyr, Trp, Phe, Met, Nle;

(e) substitution of the important Asn residue by a hydrophilic, non-charged, aliphatic natural or non-natural amino acid residue such as Gln;

(f) substitution of the Arg residue by a positively

charged, natural or non-natural amino acid residue, preferably selected from Lys, Orn, homoArg;

(g) substitution of the Trp residue by a natural or non-natural hydrophobic, aliphatic or aromatic, amino acid residue, preferably selected from Tyr, Ile, Leu, Nle, Tic, Phe, 4-phenyl-Phe, 4-methyl-Phe;

(h) substitution of the Ile residue by a natural or non-natural hydrophobic, aliphatic or aromatic, amino acid residue, preferably selected from Tyr, Phe, Leu, Nle, Tic;

(i) substitution of the Thr residue by an aliphatic hydrophobic amino acid residue such as Ala, Ile, Leu, or a hydroxy- or thio-containing amino acid residue preferably selected from Cys, Ser;

(j) truncation by up to 4 amino acid residues from either the C or N terminal;

(k) amidation of the C-terminal Thr;

(l) cyclization of **pep2** or of any peptide of (a) to (k);
and

(m) any combination of (a) to (l).

8(Previously Amended). A peptide according to claim 7, selected from:

- | | |
|--------------------|---|
| (pep2) | Glu-Phe-Leu-Asn-Arg-Trp-Ile-Thr (SEQ ID NO:1) |
| (pep15) | Ile-Val-Glu-Phe-Leu-Asn-Arg-Trp-Ile-Thr (SEQ |
| ID NO:8) | |
| (pep16) | Glu-Phe-Leu-Asn-Arg-Trp-Ile-Thr-Phe-Cys (SEQ |
| ID NO:9) | |
| (pep17) | Ala-Thr-Ile-Val-Glu-Phe-Leu-Asn-Arg-Trp-Ile- |
| Thr (SEQ ID NO:10) | |
| (pep18) | Glu-Phe-Leu-Asn-Arg-Trp-Ile-Thr-Phe-Cys-Gln- |

Ser (SEQ ID NO:11)

- (**pep19**) Leu-Asn-Arg-Trp-Ile-Thr (SEQ ID NO:12)
- (**pep20**) Arg-Trp-Ile-Thr (SEQ ID NO:13)
- (**pep21**) Glu-Phe-Leu-Asn (SEQ ID NO:14)
- (**pep22**) Ala-Phe-Leu-Asn-Arg-Trp-Ile-Thr (SEQ ID NO:15)
- (**pep23**) Lys-Phe-Leu-Asn-Arg-Trp-Ile-Thr (SEQ ID NO:16)
- (**pep24**) Glu-Ala-Leu-Asn-Arg-Trp-Ile-Thr (SEQ ID NO:17)
- (**pep25**) Glu-Val-Leu-Asn-Arg-Trp-Ile-Thr (SEQ ID NO:18)
- (**pep26**) Glu-Phe-Ala-Asn-Arg-Trp-Ile-Thr (SEQ ID NO:19)
- (**pep27**) Glu-Phe-Leu-Ala-Arg-Trp-Ile-Thr (SEQ ID NO:20)
- (**pep28**) Glu-Phe-Leu-Asn-Ala-Trp-Ile-Thr (SEQ ID NO:21)
- (**pep29**) Glu-Phe-Leu-Asn-Glu-Trp-Ile-Thr (SEQ ID NO:22)
- (**pep30**) Glu-Phe-Leu-Asn-Arg-Ala-Ile-Thr (SEQ ID NO:23)
- (**pep31**) Glu-Phe-Leu-Asn-Arg-Trp-Ala-Thr (SEQ ID NO:24)
- (**pep32**) Glu-Phe-Leu-Asn-Arg-Trp-Ile-Ala (SEQ ID NO:25)
- (**pep33**) Glu-Phe-Leu-Asn-Arg-Trp-Ile-Thr-NH₂ (SEQ ID

NO:26) and,

(**pep34**, linear) and (**pep35**, cyclic) Cys-Glu-Phe-Leu-Asn-Arg-Trp-Ile-Thr-Ala-Cys (SEQ ID NO:27).

9 (Withdrawn non-elected species). The synthetic peptide Arg-Met-Leu-Thr (SEQ ID NO:2) (**pep3**), and derivatives thereof according to claim 4, obtained by:

(a) elongation by up to 4 further amino acid residues at the C and/or N terminal end, preferably according to the natural sequence of IL-2;

(b) substitution of the Arg residue by a natural or non-natural positively charged amino acid residue, preferably selected from Lys, Orn, homoArg, diaminobutyric acid;

(c) substitution of the Met residue by a natural or non-natural hydrophobic, aliphatic or aromatic, amino acid residue, preferably

selected from Phe, Tyr, Ile, Leu, Nle, Tic;

(d) substitution of the Leu residue by a natural or non-natural hydrophobic, aliphatic or aromatic, amino acid residue, preferably selected from Phe, Tyr, Nle, Tic;

(e) substitution of the Thr residue by an aliphatic hydrophobic amino acid residue such as Ala, Ile, Leu, or a hydroxy- or thio-containing amino acid residue such as Ser, Cys;

(f) amidation of the C-terminal Thr residue;

(g) cyclization of pep3 or of any peptide of (a) to (f); and

(h) any combination of (a) to (g).

10(Withdrawn non-elected species). A peptide according to claim 9, selected from:

(pep3) Arg-Met-Leu-Thr (SEQ ID NO:2)
(pep36) Ala-Met-Leu-Thr (SEQ ID NO:28)
(pep37) Arg-Ala-Leu-Thr (SEQ ID NO:29)
(pep38) Arg-Met-Ala-Thr (SEQ ID NO:30)
(pep39) Arg-Met-Leu-Ala (SEQ ID NO:31)
(pep40) Lys-Met-Leu-Thr (SEQ ID NO:32)
(pep41) Arg-Val-Leu-Thr (SEQ ID NO:33)
(pep42) Arg-Met-Leu-Thr-NH₂ (SEQ ID NO:34)
(pep43) Pro-Lys-Leu-Thr-Arg-Met-Leu-Thr (SEQ ID NO:35)
(pep44) Arg-Met-Leu-Thr-Phe-Lys-Phe-Tyr (SEQ ID NO:36) and,
(pep45, linear) and (pep46, cyclic) Cys-Arg-Met-Leu-Thr-Ala-Cys
(SEQ ID NO:37).

11(Currently amended). A method of selecting anti-inflammatory peptides derived from pro-inflammatory IL-2, which comprises:

(i) carrying out enzymatic digestion of IL-2 with a proteolytic enzyme that participates in the breakdown of the extracellular matrix (ECM);

(ii) testing the fractions obtained in (i) for their in

vitro ability to inhibit at least one of the following processes:

(a) adhesion of activated T cells to ECM proteins; (b) chemotactic migration of T cells through ECM proteins; (c) cytokine- or mitogen-induced T cell proliferation; (d) cytokine secretion by cytokine- or mitogen-stimulated T cells; (e) spontaneous or cytokine-induced secretion of a cytokine, ~~e.g. IL-6 or IL-1 β~~ , from intestinal epithelial cells,

(iii) selecting the fractions of (ii) active in at least one of the bioassays (a) to (e), fractionating each fraction to identify individual peptides thereof, and submitting each identified peptide to sequencing and synthesis;

(iv) carrying out one or more of the bioassays (a) to (e) with a synthetic peptide identified in step (iii), and selecting those peptides that show significant inhibitory activity in at least one of the bioassays (a) to (e).

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12(Original). The method according to claim 11, wherein the proteolytic enzyme is elastase, a collagenase or a metalloprotease.

Claim 13 (Cancelled)

14(Currently amended). A pharmaceutical composition comprising at least one synthetic peptide or peptide derivative according to ~~any one of claims 1 to 10~~ claim 3, and a pharmaceutically acceptable carrier.

Claims 15-17 (Cancelled)

18(Currently amended). A method for the treatment and/or alleviation of acute and chronic inflammatory disorders comprising administering to a subject in need thereof an effective amount of an

anti-inflammatory synthetic peptide according to ~~any one of claims~~
~~1-10~~ claim 3.

19(New). The synthetic peptide of claim 4, which is **pep2**
(SEQ ID NO:1).

20(New). A pharmaceutical composition comprising the
synthetic peptide of claim 19 and a pharmaceutically acceptable carrier.

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21(New). A method for the treatment and/or alleviation of
acute and chronic inflammatory disorders comprising administering to a
subject in need thereof an effective amount of an anti-inflammatory
synthetic peptide according to claim 19.
